Special Article

BEN FRANKLIN AND OPEN HEART SURGERY

Julius H. Comroe, Jr., M.D. and Robert D. Dripps, M.D.

In 1966, President Lyndon Johnson said: "Presidents . . . need to show more interest in what the specific results of research are in their lifetime, and in their administration. A great deal of *basic* research has been done . . . but I think the time has come to zero in on the targets by trying to get our knowledge fully applied . . . *We must make sure that no life saving discovery is locked up in the laboratory* (italics added)."

President Johnson's words popularized a new set of terms: research in the service of man (implying that there are *two* types of biomedical research, one that *is* in the service of man and another that is *not*), strategy for the cure of disease, targeted research, mission-oriented research, programmatic research, commission-directed research, contract supported research, and payoff research. And the President's remarks have been summarized as "research is fine, but results are better" and "we know all we need to know: now all we must do is to apply what we already know." His philosophy led to a sharp upsurge in contract-supported research and commission-initiated research.

Most scientists are convinced that *basic, undirected research* is essential to the prevention, diagnosis, and treatment of disease, and most scientists can support their convictions with dramatic examples. (1) When Roentgen discovered X rays, it was not to enable a cardiologist to visualize the coronary arteries of a patient suffering from angina pectoris; he was studying a basic problem in physics to determine the electrical nature of matter. (2) When Karl Landsteiner discovered blood groups, it was not part of a program to make blood transfusions safe; he was investigating basic problems in immunology. (3) When Cournand and Richards passed a catheter into the heart of man, it was not to develop a new method of diagnosing congenital or acquired heart disease. They were primarily pulmonary physiologists who wanted to learn more about a basic physiological problem of how blood and air are distributed to air sacs of lungs. To do that, they first needed to measure the oxygen content of mixed venous blood

From the Cardiovascular Research Institute, University of California, San Francisco, California 94143 and The University of Pennsylvania School of Medicine, Philadelphia Pennsylvania 19174.

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in the right atrium. (4) When Shackell developed the technique of freeze-drying in 1909, it was not to preserve penicillin without loss of potency (there *was* no penicillin) or to preserve plasma and its fractions (there *were* none in 1909). He was studying a basic problem of the water content of liver and muscle of steers and needed a better method to prevent loss of water during his measurements. (5) When Clarke, a collector and amateur breeder of butterflies, studied variations in the color of butterfly wings, he had no idea that it would lead to the discovery of the Rh factor in human blood. (6) When Davies and Brink devised an electrode for measuring the partial pressure of oxygen (Po_2) it was not to monitor blood oxygen in an intensive care unit; it was to measure oxygen consumption of resting and active sympathetic ganglia.

Such "for instances" or anecdotes are fascinating but they would not convince an editor of a scientific journal that they prove the case for support of basic science (though these "for instances" would make interesting "Letters to the Editor"). Nor should "for instances" form a logical basis for a national science policy.

In 1966, the position of the Johnson Administration on basic research was bolstered by a study called *Project Hindsight*,[1] commissioned by the Department of Defense. A team of scientists and engineers analyzed retrospectively how 20 important military weapons such as Polaris and Minuteman missiles, nuclear warheads, C-141 aircraft, the Mark 46 torpedo, and the M 102 howitzer came to be developed.

Some of the conclusions of the study were that (a) the contributions of University research were minimal, (b) scientists contributed most effectively when their effort was mission oriented, and (c) the lag between initial discovery and final application was shortest when the scientist worked in areas targeted by his sponsor. Although the report stated that the study focused primarily on the physical and engineering sciences, and that only a small fraction of the technological advances analyzed could have occurred without the discovery of nuclear fission in 1939 and without the organized body of knowledge that had accumulated in physics and mathematics by the 1930's and, although only a summary was published in 1966 and a full report has not yet been published 8 years later, this brief "interim report" had a great impact on Congress and on the Office of Management and Budget, because it was a *study* and not another "for instance."

Medical and other scientists countered *Project Hindsight* with some carefully prepared case studies. Shannon[2] wrote one on the development of polio vaccine (1966); Visscher[3] wrote one on the development of rubella vaccine (1967); Deutsch et al[4] analyzed advances in the social sciences (1971); and Holton[5] traced research in one aspect of physics (shock waves) in 1973. The National Science Foundation commissioned two studies: a 1969 study by the Illinois Institute of Technology[6] that included only one case report on a biomedical advance—how oral contraceptives came about, and a 1973 study by Battelle Laboratories[7] that also included an analysis of only one biomedical advance—the cardiac pacemaker. And in 1974 Kone and Jordan edited *The Greatest Adventure: Basic Research that Shapes Our Lives.*[8] But a continuing weakness in all of these studies or stories was that the authors analyzed "for instances" that they themselves had selected.

So it seemed to us that we, as scientists—despite strong personal convic-

tion—have little objective data on how lifesaving advances in medicine and surgery have come about, and it's time to collect it. We became convinced that it was more important for us to do *research on research,* on the *process* of discovery, than it was for us to continue with our ongoing research or other interests. We soon learned that research on research is more difficult than conventional laboratory research, takes a much longer time, and presents unusual problems in achieving objectivity. And we learned that an initial research project in this field, as in other fields, leads to many projects. So, we're far from finished, and we have no Results to present and no Conclusions to draw at this time. But we would like to present the design and the goals of our main project, invite your criticism, advice, and help, and tell you some interesting things that we have learned (that won't ever fit into the Results or Conclusions of our final report).

A. DESIGN OF THE PROJECT

We wanted to learn how clinical advances came about that *directly* prevented disease, cured or arrested disease, or decreased suffering and prolonged useful life. We believed that it was essential to avoid using the anecdotal approach, which inevitably leads to bias. Therefore, we decided to look at a large field, and we selected "Advances in cardiovascular and pulmonary medicine and surgery since 1945." To avoid stacking the cards to favor the contributions of basic research, we asked *physicians and surgeons* to pick the most important *clinical* advances since 1945 that directly benefited their patients. Here are their "Top Ten" (Table 1).

At this time, we will discuss only one of the top ten, open heart surgery, because it headed the list of almost every voter. However, the discussion that follows applies equally well to each of the other nine advances.

The public knows about open heart surgery. To the public, it is *the* dramatic achievement, the pinnacle of surgery, comparable to the conquest of Mt. Everest (Fig. 1). There are two ways the cardiac surgeon could have reached the top of Mt. Everest. The first is one giant leap from sea level to the pinnacle. The second is a less dramatic walk up the back of the mountain (Fig. 2), up steps laboriously chiseled out by thousands of workers in many branches of science (physical, biological and clinical) over tens or hundreds of years.

Stated very briefly, our main project has three goals. (1) We want to find out whether the cardiac surgeon took a giant leap up the front of the mountain or whether he walked up the back. (2) If he walked up the back to or almost to the top, we want to learn *who* built the steps and *why? Was Cardiac Surgery their target?* (3) We want to tell the public and especially the makers of public policy how he got there.

(1) *A Giant Leap?*—Our approach had to be retrospective. We started with the fact of open heart surgery and worked back, always asking the same question in one form or another: What had to be learned before the next step could follow? For the final step, the question was: What had to be learned before the operation could become a routinely successful procedure? Most surgeons would answer that the *laboratory* was an absolute requirement, but what they really mean is the surgical dog laboratory

where surgeons practice and perfect their skills. These techniques are, of course, important, but what we need to know is: What *knowledge* had to be acquired before open heart surgery could become a routinely successful procedure?

One absolute requirement was the development of a pump-oxygenator to keep the patient alive while his own heart was being repaired. The pump-oxygenator was developed by a surgeon, John Gibbon. For 15 years it was a product of mission-oriented research, and then, for the last few years, of engineering and development. But now our question becomes: What had to be learned before Gibbon could even think of building a pump-oxygenator, let alone construct a dependable device? It is crucial that the public and maybe also medical students, physicians, and surgeons realize that the pump-oxygenator was itself possible only because of many earlier discoveries.

TABLE 1

THE "TOP TEN"

Open heart surgery
Cardiac resuscitation, defibrillation, cardioversion, pacing
Intensive cardiovascular and respiratory care
Chemotherapy and antibiotics
Vascular surgery
Medical treatment of coronary insufficiency
Oral diuretics
New diagnostic methods
Drug treatment of hypertension
Prevention of poliomyelitis

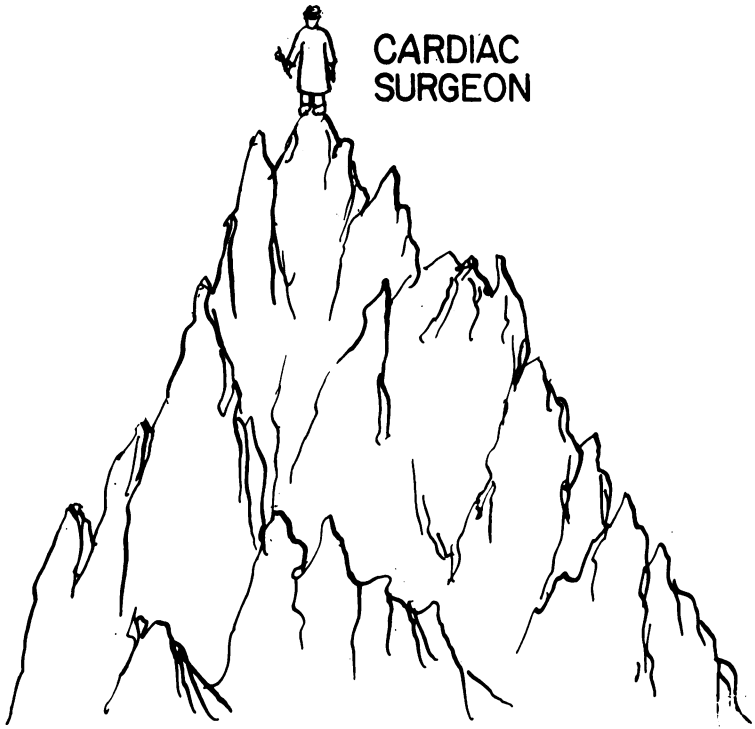


Fig. 1. One giant leap to the pinnacle?

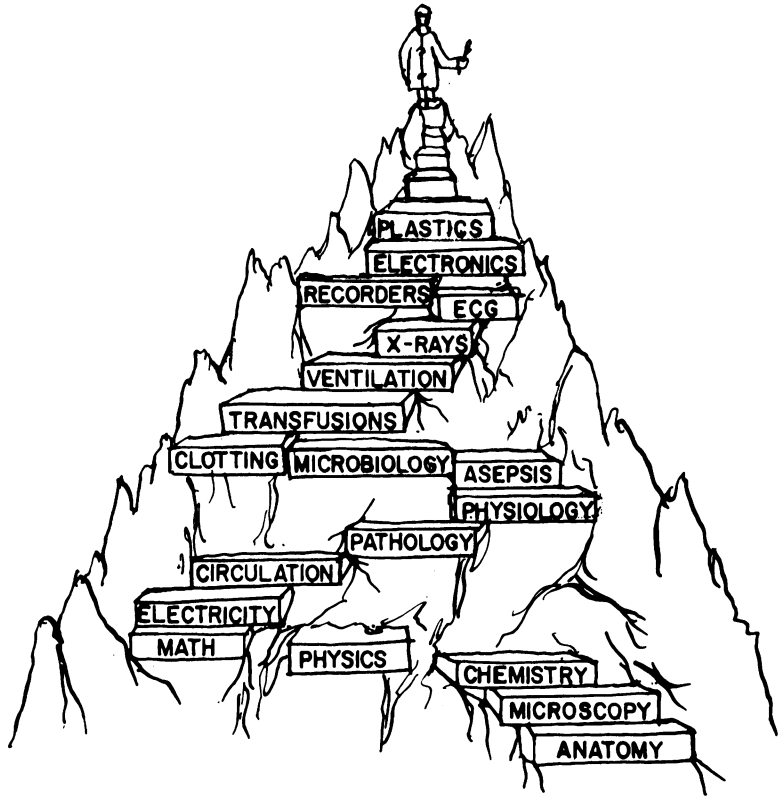


Fig. 2. Or did he climb the steps up the back of the mountain?

One of the necessary earlier discoveries was that of two anti-coagulants: citrate, which was discovered immediately following the basic discovery of the role of calcium in blood coagulation, and heparin, which was discovered during a basic physiological investigation of blood clotting. Gibbon didn't begin his work on pump-oxygenators until 1934—the year that pure, potent heparin became available. This timing was not a coincidence; the most elegant pump that could be devised by engineers was doomed to fail unless the blood it pumped remained liquid. Another necessary earlier discovery was that of blood groups by Landsteiner; this led to blood typing, then to safe blood transfusions, and now to safe blood for use in pump-oxygenators. A third earlier discovery uncovered basic knowledge of red blood cells, their life span in the body and how to preserve them outside the body; this led to the ability to store blood for use in emergencies, then to blood banks for routine convenient use, and now to adequate supplies of compatible blood for use in the pump-oxygenator.

A fourth yielded basic information on the diffusion and exchange of O_2 and CO_2 that provided an essential base for the construction of artificial oxygenators. A fifth was the synthesis of new plastic materials, which began in chemistry laboratories in 1905. Ultimately, this permitted the development of plastic tubes, bags, and valves, which are absolute requirements for a pump and valves that will damage blood little or not at all, and of an artificial lung that will permit proper passage of oxygen and carbon dioxide.

But successful open heart surgery requires more than the use of a pump-oxygenator. So our question now becomes: What had to be learned to permit the cardiac surgeon to open the thorax, stop the heart, open the heart, restart the heart, and care for the patient to ensure full and speedy recovery?

(a) Physiologists had to learn about the existence and function of the heart's conducting system and the normal rhythm of the heart. Cardiologists had to study abnormal rhythms, especially ventricular fibrillation, which, if not reversed, leads to death in a few minutes. These studies led to the technique of electrical defibrillation and to other devices now used to detect serious arrhythmias, to reverse them ("cardioversion"), or to control them (cardiac pacemaker). (b) Physiologically trained anesthetists had to develop closed-circuit anesthesia and learn to use muscle-relaxing agents that allowed careful, delicate, painstaking repair of cardiac tissues to replace lightning-fast slashing and stitching that was the hallmark of early cardiac surgeons. (c) Physiologists had to learn about control of respiration and mechanical properties of lungs, how to ventilate lungs when the thorax was open, and how to measure blood oxygen (O_2), carbon dioxide (CO_2), and acidity (pH). Only then could there be precise oxygenation of the patient's blood and proper removal of CO_2 during the operation and later in the intensive care unit (which itself was based on years of fundamental physiological research on the heart, lungs, and circulation). (d) A German physicist, Roentgen, had to discover X rays, a Dutch physiologist, Einthoven, had to devise a sensitive instrument to record the electrocardiogram (ECG), and a French and American physiologist had to develop the technique of cardiac catheterization, all essential to accurate preoperative diagnosis. (The history of cardiac surgery includes many optimistic starts followed by abrupt stops. These stops were usually due to the death of a patient because an inaccurate preoperative diagnosis

forced the surgeon to face an unsuspected lesion that he was not prepared to deal with.) (e) Physiologists and clinicians had to study the survival times of completely bloodless organs at normal and low body temperatures, so that cardiac surgeons would know the safe time limits for an operation with the heart stopped. (f) Physiologists had to learn how to stop the heart beat chemically or electrically. Ultimately this knowledge permitted cardiac surgeons to stop a human heart and have a bloodless, motionless heart on which to operate, with assurance that this heart would beat again when the surgeon was ready and that its beat would be normal and vigorous. (g) A new type of scientist, the microbiologist, had to discover bacteria (which first had to await the discovery of the microscope), and many scientists had to do basic research on specific infections, asepsis, antiseptics, chemotherapy, and antibiotics.

It seems certain, therefore, that the cardiac surgeon did not reach the pinnacle in one giant leap but climbed the steps carved by thousands of earlier workers up the back of the mountain.

(2) *Who Built the Steps and Why?*—Table 2 lists 25 bodies of knowledge that had to be developed to permit just one clinical advance—uniformly successful open heart surgery. For all ten clinical advances listed in Table 1, we have identified about 150 essential bodies of knowledge. But each of these 150 is only a heading of a word or two. Under each heading (e.g., electrocardiography in Table 2) is a long history of scientific progress from earliest concepts to full and effective use (for example, ECG) as a routine diagnostic test.

With the generous help of consultants, we have identified about 3,000 scientific reports judged to be necessary for the development of the 150 bodies of knowledge. Of these, we plan to analyze in detail the 500 individual research reports judged by consultants to be the most important, most decisive, and most crucial for the full development of the ten clinical advances. From this analysis, we will learn how and why each study was done, how each led to the next step, how many studies were undirected and produced knowledge now essential but initially unrelated to its present clinical use, how many studies were mission oriented specifically to prevent or cure one disease, how many were reports of advances in engineering that created or improved needed instruments, apparatus, or techniques, and how many key, decisive studies were designed by commissions or supported by contracts.

(3) *Tell the Public and the Makers of Public Policy What We Have Learned.*—The public usually knows only the final product of research and development, because it is easy to identify and publicize. And, as a rule, the public tends to link the name of one man with one discovery, e.g., the radio with Marconi or the airplane with Wright. What the public does not know is that tens, hundreds, and thousands of studies, stretching back over decades or centuries, contributed to any one step up the mountain. For example, Table 2 lists the word electrocardiography. The public knows ECG, but it does not not connect the ECG with studies by Benjamin Franklin, the colonies' foremost scientist, who learned in 1752 that naturally occurring lightening and electricity stored in a battery (initially a Leyden jar) are one and the same; or with studies by Galvani and Volta, whose curiosity about "animal electricity" in the late 1700's led to the science of electrophysiology and also to the intensely practical development of the

TABLE 2

TWENTY-FIVE BODIES OF KNOWLEDGE ESSENTIAL FOR THE FULL DEVELOPMENT OF OPEN HEART SURGERY

Anatomic and clinical diagnosis
Physiological diagnosis: electrocardiography
Physiological diagnosis: cardiac catheterization
Radiologic diagnosis: selective angiocardiography
Transfusion, blood groups and typing, blood preservation, components of blood and plasma
Nutrition, intravenous feeding
Preoperative care
Assessment of cardiac, pulmonary, renal, hepatic, and brain function
Asepsis
Monitoring ECG, blood pressure, heart rate, blood O_2, CO_2 and pH, and EEG
Anesthesia and neuromuscular blocking agents
Hypothermia and survival of ischemic organs
Ventilation of open thorax
Anticoagulants
Pump oxygenator
Elective cardiac arrest, defibrillation
Fluid and electrolytes, acid-base balance
Surgical instruments and materials
Surgical techniques and operations
Relief of pain
General principles of intensive care
Chemotherapy and antibiotics
Management of postoperative complications
Management of heart failure
Wound healing

storage battery; or with studies by Keith, Flack, His, Tawara, and Purkinje, who learned how the impulse that sparks the heart beat originates in the sinoatrial node and spreads to the atria and the ventricles; or with studies by Waller and Einthoven, who developed the ECG at the end of the nineteenth century; or with work by Sir Thomas Lewis, who used the ECG extensively as a physiological and diagnostic tool to learn much of what we know of normal and abnormal rhythms of the human heart, or with research by Wilson, who used the ECG in 1930 to diagnose myocardial infarction.

Another problem with public understanding of science is that some of the great advances have been around so long that they've become part of everyday life. Who today thinks of fire, or the wheel, or electricity, or the flush toilet as the product of truly creative minds? Who today still thinks of penicillin as a wonder drug? Now it's something — like toothpaste — that you buy at a drug store. The public has long forgotten that the discovery of penicillin first required the development of whole new sciences of microscopy, microbiology, infectious diseases, and pharmacology.

Cardiac catheterization is now an everyday routine test. Physicians and patients think of it only in terms of a patient lying on a hard table with a long plastic tube in his heart. What a cardiac catheterization laboratory actually needs and uses besides a patient, a catheter, a cardiologist, and a nurse is shown in Figure 3. The public forgets or was never told that cardiac catheterization is not a procedure that stands alone; its use depends on many advances in the basic sciences, in clinical investigation, in engineering, and in industrial development.

In 1969, Robert Berliner said: "Above all we have an enormous job of education to do. We need far more general understanding of how science progresses, of the tortuous paths from distant, unrelated points of departure that converge to bring us where we are. When the press conference is held to announce the current achievement, we need less emphasis on wild speculation about unforeseeable applications and far more on the roots in the past. We need emphasis not only on the giants on whose shoulders we have stood, but on the contributions of unsung investigators too numerous to mention. We should have the equivalent of a brief 'commercial' before each therapeutic measure, each dose of vaccine, each effective drug: 'This is made possible by the research of Whozis and So and So; we trust you will find it effective and remember what research has done for you.' "

B. SOME THINGS WE HAVE LEARNED

(1) Physiologists can be proud of their contributions to medical science. In the field of cardiac surgery, they showed how to ventilate the open thorax; how O_2 moved from air to lungs to blood to tissues; how to measure Po_2, Pco_2 and pH.

Physiologists learned how to keep blood from clotting and how to preserve this liquid blood for several weeks. They learned how the heart beat spread from the sinatrial node to the atria and the ventricles. They devised and used the first ECG. They first used the cathode-ray oscilloscope to measure electrical events in animals—an apparatus now essential for all monitoring in operating rooms and intensive care units. Physiologists

CATHETERS

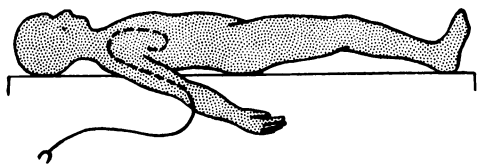
1 Dacron and nylon weave
2 Radiopaque cloth woven
3 Opaque synthetic extruded tubes for catheters
4 Double lumen, balloon tipped
5 Dotter-Lucas, Rashkind, Swan-Ganz
6 Spring wire guides
7 Cournand-type needle for percutaneous insertion
8 Platinum tip catheters for H_2 or ascorbate curves
9 Pacing catheters
10 Phonocardiographic catheters
11 Catheter tip pressure transducer
12 Fiber optic catheter

STERILE EQUIPMENT

1 Steam sterilizer
2 Ethylene oxide gas sterilization
3 Benzalkonium and cyanide solutions
4 Sterile brushes, tapes, etc.
5 Scrub and preparation solutions

DRUGS AND CHEMICALS

1 Sedatives
2 Local and general anesthetics
3 Oxygen (with tubing, masks, valves, tanks)
4 Antiarrhythmic drugs
5 Indocyanine green for dye dilution curves
6 Radiopaque contrast media
7 Sterile solutions
8 Antibiotics
9 Heparin
10 Acetylcholine
11 Isoproterenol



ROENTGENOGRAPHIC EQUIPMENT

1 X-ray tube
2 Electronics for pulsing
3 Image intensifier
4 Television camera and monitor
5 Video tape recorder
6 Disc-type video storage
7 Biplane cine camera
8 High contrast cine film
9 Projector for still and motion pictures
10 Timing of X-ray pulses and cine exposure
11 Lead sheets and aprons for protection

ELECTRONIC INSTRUMENTS

1 Multichannel recorder
2 Transducers and amplifiers for ECG, blood pressure, phonocardiograph, polarograph and heart rate
3 CRO for monitoring
4 FM tape recorder and tape
5 Thermistor probe
6 Oximeter
7 Densitometer
8 Defibrillator
9 External and internal pacemaker

CALCULATORS

1 Slide rule
2 Calculator
3 Computer

SPECIAL ITEMS

1 Microsyringes
2 Pressure injector for angiography, timed to match cardiac cycle
3 Respiratory valves and spirometers
4 Douglas bags for collecting gas
5 Gas sample collectors
6 Disposable syringes, stopcocks and plastic tubes
7 Surgical instruments for macro and micro dissection
8 Constant withdrawal-infusion syringe

Fig. 3. Cardiac catheterization requires more than a catheter and a table.

learned how to measure blood pressure, cardiac output, blood flow and how to evaluate cardiovascular function. A physiologist, Carl Wiggers, introduced the concept of the vulnerable period of the ventricles and so provided the scientific base for defibrillation, "cardioversion," and cardiac pacing.

Equally important, many physiologists contributed to the scientific training of modern surgeons who then applied their training to solve clinical problems. John Gibbon spent three and a half years (1931-1934) practicing surgery half of the time and doing research with Eugene Landis the other half; this was just before Gibbon started work on the pump-oxygenator in 1934. Landis, with characteristic modesty, says that his contribution to Gibbon was "transmitting what he (Landis) had learned from Cuthbert Bazett, Merkel Jacobs, A. N. Richards, Thomas Lewis, and August Krogh." We add, what a wonderful way to start a career in surgical research!

(2) Research on physiological problems has had important spin-offs to other fields. Studies on animal locomotion by Muybridge in 1872 produced the first motion pictures (on glass plates); this development led to Edison's use in 1893 of a celluloid strip, which then became the basis of a huge motion picture industry. Research by earlier physiologists on the mechanism of the heart beat in frogs and turtles led Einthoven to devise a sensitive string galvanometer, which was then used in Holland for recording wireless signals from the Dutch East Indies, for sound ranging in World War I to detect the location of German guns on French battlefields, and for telemetry. The need to completely denervate the carotid arteries of the dog to study responses of denervated arteries to chemical agents led in 1960 to the technique of microvascular surgery and now to reconstruction of a ligated vas deferens. The Po_2 electrode, developed entirely for neurophysiological use, is now widely used to measure pollution of streams. Studies on the water content of tissues by Shackell (1909) led him to develop the technique of freeze-drying, which now has many industrial applications, the latest being a large instant coffee industry. Research on blood groups for safe use of blood has had important spin-offs in such diverse fields as human genetics, determination of paternity, criminology, and anthropology.

(3) Physiologists in their research have both benefited other disciplines and in turn benefited from them. There are many instances of discoveries bouncing back and forth from *basic* to *applied* sciences to the benefit of both. Studies on animal locomotion (basic) led to the motion picture industry (applied), later to biplane cineangiocardiography for research (basic) and clinical diagnosis (applied), and now to the study of the velocity of contraction of cardiac muscle (basic). The urgent need in World War II for a device to detect leaks in aviators' oxygen masks led a physiologist, John Lilly, to devise a nitrogen meter (applied), using knowledge developed in earlier research in physics (basic). The new meter was soon used to study distribution of gas to alveoli (basic) and a little later to test pulmonary function clinically in patients suspected of having cardiopulmonary disease (applied). Now it is also being used to study the mechanism of airway closure (basic) with the expectation that a new test will result to permit earlier diagnosis (applied). Studies on the cause of irregularities in the capillarity of mercury (basic) led Heyrovsky to devise a dropping mercury test that in turn led to the polarograph, an instrument useful in detecting small quantities of metals (applied). This discovery led

to the O_2 electrode used to measure Po_2 in autonomic ganglia (basic) and, in turn, to the blood O_2 electrode now used universally to monitor the ventilation of patients in operating rooms and in intensive care units (applied) and to detect stream pollution (applied).

(4) Scientists do their research for a wide variety of reasons. John Gibbon did his because a patient died of pulmonary embolism; he wanted to devise an apparatus to bypass the lung and allow him to remove the embolus (he did *not* have open heart surgery in mind). Julius Jacobson, the father of microvascular surgery, was asked by two fellow faculty members at Vermont if he could perform a guaranteed total denervation of the carotid arteries of the dog so that they could test the responses of completely denervated vascular smooth muscle to drugs. The only certain way was for Jacobson to cut the artery in two and then stitch it together again. This procedure required use of a dissecting microscope and led to the birth of microvascular surgery.

Dennis Jackson, a physiologist who later turned pharmacologist, developed the first closed-circuit anesthetic equipment in 1915 to help the poor. Jackson later discussed his motives: "The need for some cheap, easy and effective method for administering nitrous oxide was impressed upon me long ago when I was a medical student on Chicago's old West side. There . . . poverty . . . mingled with the stench from the stockyards. Many patients came into the clinic for minor surgery. Nitrous oxide was the anesthetic of choice, the cost being fifty cents. But that fifty cents often meant that the patient could not eat for the next day or two . . . Nitrous oxide was generally given without oxygen . . ." Because added O_2 cost twice as much and that meant no food for 4 days!

Jay McLean, a University of California college student, wanted a career in academic surgery and determined in 1915 to leave the University of California at Berkeley to enter the Johns Hopkins School of Medicine even though he had not been accepted. On his arrival in Baltimore, the dean accepted him for admission a year later. McLean asked Professor William Howell for a year of research in the physiology laboratory "to see if I could solve a problem by myself." Howell put him to work on brain cephalin (a clotting factor). McLean instead discovered heparin in liver.

Charles and Scott (Toronto) decided to purify heparin in 1933, not because of demand for its use clinically but "because of the importance of heparin in certain physiological experiments." Hustin in Brussels in 1912 had a patient who died of carbon monoxide (CO) poisoning. Hustin reasoned that he could have saved the patient's life if he could have bled him, removed the CO, added O_2, and then reinjected the blood. But this procedure required blood that would not clot. He had spent a year in the physiology laboratory at the University of Brussels, unusual for a young physician, and had perfused organs with defibrinated blood. Because defibrinated blood had some toxic effects, he experimented with the addition of citrate and so developed the first indirect blood transfusion. (Remember that in the early 1900's the great American surgeon, Crile, was transfusing blood directly from an artery of a donor to a vein of the recipient; the two vessels were sutured end to end for the duration of the transfusion). Carrel (more of him later) developed vascular surgery because he wanted to study the individual metabolic requirements of each organ: he wanted

to know what each organ needed for maximal survival and optimal function.

Sometimes one cannot tell from reading his report why a scientist began his studies. Maybe he thought it unscientific to say why. Maybe an editor deleted his account. Maybe the scientist stumbled or blundered on his discovery and didn't want to say so. Maybe he was a young scientist reluctant to acknowledge his debt to others. Sometimes a scientist in later years tells us how he came to make his early discoveries. Gibbon did this for the pump-oxygenator; McLean did it for heparin; one physiologist does this each year in the prefatory chapter of Annual Reviews of Physiology.

(5) We have also learned that the record has not been entirely good. True, X rays were put to physiological and clinical use almost instantly; Roentgen's first report was in December 1895 and within a few months, in 1896, there was already a new journal (*Archives of the Roentgen Ray*) and within a year a new society (The Roentgen Society) devoted completely to the new rays. The electrocardiograph too was put to clinical use quickly after Einthoven's work. But many discoveries made and widely used in the laboratory (such as artificial or controlled ventilation, measurement of lung volume, ventricular defibrillation and closed-chest cardiac massage) were not quickly applied clinically.

Vesalius demonstrated artificial ventilation in 1543, Hooke demonstrated it again in 1667, and physiologists used it in laboratory experiments in the nineteenth century, but it never crossed over to clinical medicine, even to ventilating the lungs of patients with an open chest, until 1915. Humphry Davy in 1800 prepared his own hydrogen, breathed it in and out, measured its concentration in the expired gas and calculated his lung volume. However, his method was not used again until the 1940's and 1950's. In 1899, Prevost and Battelli produced ventricular fibrillation electrically and then defibrillated the same dogs with stronger shocks. Their work had no impact until 1930 when Howell translated their paper into English for Donald Hooker and William Kouwenhoven who were then working on electric shock in Howell's physiology laboratory at Hopkins. Closed-chest cardiac message has been widely used in physiology laboratories since 1878 to resuscitate cats and dogs, but it was not applied to man until 1960. Long lags also occurred before the full clinical use of heparin, hemodialysis, the cathode-ray oscilloscope, telemetry, and techniques of vascular surgery.

One of the most remarkable of all lags was that in vascular surgery. Between 1902 and 1910, Alexis Carrel performed every feat and developed every technique known to vascular surgery today (except for using a dissecting microscope and plastic tubes, neither of which had then been discovered), but his work was essentially lost until 1940. He reunited vessels intima to intima; he sutured artery to artery, vein to vein, artery to vein, end to end, side to side, and side to end. He used patch grafts, autografts, homografts, heterografts, rubber tubes, glass tubes, metal tubes, and absorbable magnesium tubes. He devised his own nontraumatic needles, clamps, and sutures. He performed a coronary bypass operation on a dog using a preserved carotid artery; the procedure required only 5 minutes. He preserved vessels, tissues, and organs by refrigerating them in Locke solution. He suggested using a segment of a patient's vein to replace a damaged artery. He transplanted thyroid, spleen, ovaries, limbs,

and kidneys and so proved that, surgically, it was possible and easy to transplant organs. But he recognized that a homograft vessel served only as a framework for new cell growth. And as early as 1912, he stated: "But it is not yet known whether surgeons will ever be able to perform a homoplastic transplant with permanent success . . . it will only be through a more fundamental study of the biological relationships existing between living tissues (. . . to recognize individuals, if such exist, between whom organs can be interchanged with impunity) that the problems involved will come to be solved."

We must ask why his work was not mentioned in the classic reports describing the "new" vascular surgical operations in the 1950's. Was Carrel's work published in a rarely read foreign language like Jansky's work on blood groups? No, he published in English. Did he work in unknown laboratories? No, he worked first at the University of Chicago and then at The Rockefeller Institute in New York City. Did he publish in journals never read by surgeons? No, he published in *Surgery, Gynecology and Obstetrics, Journal of the American Medical Association,* and *Annals of Surgery.* Was his research held in low esteem? No, he won the Nobel Prize in 1912, the first American to receive the Nobel Prize in Medicine and Physiology.

Such lags probably occur in every branch of science and in technology, not just in biomedical research. It is such lags between initial discovery and application to patient care that support the clamor for commission-directed research and contract-supported research and development.[9] It is our responsibility to try to interest clinicians in our ongoing work and its possible applications to medicine, even though our attempts will not always work. Wiggers (*American Heart Journal,* 1940) fibrillated and defibrillated the heart of the same dog 41 times and then "by lecture and demonstration attempted to acquaint laboratory workers and surgeons with the procedure" of electrical defibrillation, but he was without success until 1956.

As you can see, research on research, like laboratory research, leads to many more questions than the initial one. What accelerated discoveries? What held them back? Could the delays have been prevented? Why didn't a scientist follow through with his initial discovery? Was it lack of interest? Was it because he didn't appreciate the importance of his work to *his* field? Was it because he didn't appreciate the significance of his work to *other* fields? Why didn't he get his ideas to others who would follow up on them? (By sharing his ideas with others? By speculating to help those with less imagination?) What would modern policies governing research have done to the research of 30-75 years ago? What would have been the effect of the Food and Drug Administration, the committee on human experimentation at each university. NIH study sections, NIH task forces, and of commissions? When might directed research have paid off? When might it have failed?

REFERENCES

1. Sherwin CW, Isenson RS: *First Interim Report on Project Hindsight.* Washington, D.C., Office of Director of Defense Research and Engineering, June 30, 1966 (Revised October 13, 1966)

2. Shannon JA: NIH: Present and potential contribution to application of biomedical knowledge. In *Research in the Service of Man: Biomedical Knowledge, Development and Use.* U. S. Senate 90th Congress, 1st Session, Document No. 55, 1967, pp 71-85
3. Visscher MB: Applied science and medical progress. In *Applied Science and Technological Progress.* National Academy of Sciences Report, 1967, pp 185-206
4. Deutsch KW, Platt J, Senghass D: Conditions favoring major advances in social science. Science 171:450-459, 1971
5. Holton G: Models for understanding the growth of research. In *The Thematic Component in Scientific Thought.* Grad J 9:397-430, 1973
6. *Technology in Retrospect and Critical Events in Science.* Prepared for the National Science Foundation by Illinois Institute of Technology Research Institute under Contract NSF-C535, December 15, 1968, and January 30, 1969
7. *Interactions of Science and Technology in the Innovative Process: Some Case Studies.* Prepared for the National Science Foundation by Battelle Laboratories under Contract NSF-C667, March 19, 1973
8. Kone EH, Jordan HJ (editors): *The Greatest Adventure: Basic Research That Shapes Our Lives.* New York, The Rockefeller University Press, 1974
9. Comroe JH Jr: What's locked up? Am Rev Resp Dis 110:111-114, 1974